March 23, 1953

Dear Kim:

This letter concerns the Neurospora UV-inactivation mss. I enjoyed reading them very much, and thank you for giving me the opportunity. I must apologize for taking so long about it , but have been so busy as to suffer from a sort of immunological paralysis: so many things to deal with that I don't know what to do first, and therefore tend to do none.

I can't help but offer some suggestions about the ms. These in no way detract from my enthusiasm about it, and are offered for whatever disposition you choose (including file 13). I showed the papers to Crow-- perhaps putting him on the spot. However, he says he enjoyed them, and would like to see them put in proper form and submitted for consideration by Genetics. He can hardly guarantee acceptance, as this will depend on the reviewer's comments, but my own suspicion is that if suitably amended the mss. will have no trouble getting into Genetics. Their publication schedule now is somewhat improved, and demands only a little patience. If youaare more in a hurry, you might send them to Szilard (i.e. & Novick) or Tatum for submission to PNAS. I think Max' peremptory refusal is ahly another of several examples of personal prejudice. I don't understand why Doby should have been so negative, unless he didn't understand them himself. Frahkly, though, I suspect that Norman's opus probably deserved and bore the brunt of adverse criticism. I'm not too happy about that paper myself, and I wonder if you would not be wiser to rely on his Exp. Cell Research as the documentation for the kinetics, and not tie your own paper with his. At any rate, I have not studied his paper nearly so closely as yours, and can say very little about it.

Some minutiae:

p1 L-12 "it seems preferable" to what? *the findingsare most simply explained....* **are suggested forms

21 *nuclei. It involves...* 22 "carrying" *that carry*

2 2 "The method..." * Such mutations are detected in a heterokaryon...*

TERMINOLOGY: general The Stanford group has made the very sensible suggestion that the technical name for the biochemical mutants should be ornithine rather than ornithineless. In any case, for GENETICS the mutant symbols should be italicized, and I would recommend the Stanford suggestion, (just as one says eosin, scute and not necessarily eosin-eyed, scute-haired etc). Also, to turn to rhetoric, "shows growth" is an awkward and unnecessary circumlocution for*grows*, as *grows normally* for"shows normal growth".

2 18 reference to sorbose effect (Tatum et al, Science....)

3 12 "if they are also homokaryotic for any recessive" *if they carry any...* ** is less cautious, but the exception is adequately stated in the next paragraph, infra.

3 13-14 A more explicit definition may be necessary to justify "recessive", although this is implicit in "heritable": *lethal when homokaryotic, but is maintained and inherited when heterokaryotic. The question...*

21-25 Not clear whether you say that you will almost always miss lethals in your initial test whenever there are two or more amycelial nuclei (as non-homologous mutations in each should permit amycelial segregants still heterokaryotic for one or more lethals. In a more complete account, as for Genetics, the point should be detailed, but in a later section. (This should also review the question, bound to come up in the readers' minds how well the distribution of nuclear types agrees with a random sampling.) You might, of course, detect lethals in these cases by a later testing of the products of a first plating, but this would also raise questions of delayed & fractional mutations which have likewise no hypothetical bearing on hypothesis (1).

4 paragraph after equations. I am sure I understood this myself, but am unable to tell how much previous experience helped. An insertion to explain "lowest possible theoretical values of P" as the lowest that can be achieved by adjusting free parameters might help. Or *The estimate of P, based on survivorship, assumes that all lethal effects are due to mutation, and all deviations....* *..ruled out if the measured numbers of mutations are too small to be reconciled with the least value of P that can be obtained by adjusting the free parameters m and n* It might help to give different symbols to the P*of (2) and of your direct estimate, to avoid repetitious language. You could then write that P* ≦ P, and that no reasonable value of n and m will in fact give P = P*. Hyp.(1) can only be ruled out by your test, not most decisively— your language simply transfers the emphasis to "lowest possible theoretical estimate".

5 3-4 I may have prejudged: how do you define homology here! This is already out of the bounds of the hypothesis, i.e., all of the units are homologous.

In figure 1, to clarify the symbols, add m=1, m=10. How is abcissa plotted?

6 7 Is this entirely independent of the distribution of nuclei?

7- and table 1. The arrangement of this table is rather difficult to understand. It would help to have a line for the unirradiated controls giving the actual proportions of the untreated conidial types. This is implied in table 2, but not clearly referred to table 1. The heading "expected survival" will be uninformative by itself, *survival expected according to (8)*. Rather than "observed/expected", it might be better to have two columns: *Observed survival, S/M*, and *S/M calculated from (8)

8 16 Would replica plating help? 13: does preponderance of pnt vitiate the precision of Exp. II?

P2. that

P2 may not be stated with utmost clarity *conidia which gave heterokaryons on minimal showed an effect of UV by tending to become homokaryotic on lysine medium, when first plated. Last sentence is too anticipatory *possible explanations will be considered later*/

(Would you want to mention the very similar haploidizing effects on diploid coli: CSH 16:428-429?)

These minutiae are not very important: the work as a whole is superb.

Of several possible courses, if I may add a (gratuitous?) recommendation, I would suggest rewriting the paper slightly more expansively (especially in the prsentation of the exptl data) for Genetics. I would include everything in this paper, and would add enough of your subsequent homology tests (as anticipated in the Biol Bull abstract) to show that m is certainly larger than 1. The detailed study of the lethals and their homology, as you are now doing, can safely be left for a later paper, but should not delay the publication of this one. If you let it go too long you will be left with an unmanageable mass that will be very difficult to digest.

Sincerely